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Introduction

This award has funded the development of a multidisciplinary prostate cancer research consortium at Emory University. During the funding period a consortium has been developed and matured. The specific research projects funded have all been successful with resultant publications and NIH grants as tangible evidence of progress and success. In addition, the dynamic prostate cancer research supported by this award has aided in the recruitment of one of the largest and most well recognized prostate cancer research groups to Emory (Dr. Leland Chung and his associates). In part because of the research environment created by this award, another key recruit has just been completed in the Department of Pathology (Dr. Milton Datta) further enhancing our capabilities in translational prostate cancer research. Since the funding of this award, Dr. Petros has been awarded an RO1 and a project in a PO1 based directly upon work funded by this Department of Defense center award. Dr. Lambeth has been awarded an RO1 similarly based upon DOD funded work. Fundamental new knowledge has been generated in the areas of mitochondrial DNA mutations in prostate cancer, reactive oxygen signaling in prostate cancer and the importance of MUC-18 in prostate cancer metastases. There are multiple publications from each of the three projects funded documenting this new knowledge. In summary, the goals of this award have been accomplished with grants and publications as tangible documentation of this success.

Body and Key Research Accomplishments

The project, now completed (including one year no-cost extension) has had essentially all of the findings published. These manuscripts constitute the bulk of the reportable outcomes and constitute the scientific report required for this final report.

The project included a pathology and technology development core, the accomplishments of which are reported in #1 below. Project #3 involved MUC-18 in prostate cancer and is summarized in #2 below. Project #1 involved reactive oxygen and NOX (previously Mox) enzyme expression and is summarized in #3 below. Project #2 involved reactive oxygen and novel tumor signatures which are reported in #4-6 below. This includes the discovery of a new candidate oncogene and a new candidate tumor suppressor gene.

1. Development of technical capabilities to support translational prostate cancer work.

- a. Dr. Amin developed a method for procuring specific populations of viable human prostate cancer cells for research (Reference 2, attached as appendix).
- b. Dr. Amin developed methodology for analysis of immunohistochemical analysis of prostate biopsies (References 8 and 9, attached as appendix).
- c. Dr. Petros developed methodology for automated sequencing of complete mitochondrial genomes from laser capture microdissected (LCM) prostate samples (Reference 12, attached as appendix).
- d. Dr. Petros developed methods for high efficiency transfection of prostate cancer cells using electroporation (Reference 1, attached as appendix).

2. Analysis of the importance of the cell adhesion molecule MUC-18.

- a. Drs. Wu, Petros and Amin described the expression patterns of MUC-18 in clinical prostate cancer specimens (Reference 4, attached as appendix).
- b. Drs. Wu, Petros and Amin cloned the MUC-18 gene and correlated expression levels with malignant progression (Reference 5, attached as appendix).
- c. Dr. Wu demonstrated that ectopic expression of MUC-18 increased metastatic potential of prostate cancer cells (Reference 15, attached as appendix).

3. Analysis of the importance of NOX enzymes in prostate cancer.

- a. Drs. Arnold, Lambeth and Petros demonstrated that hydrogen peroxide mediates the transforming properties of Nox in prostate cancer (Reference 3, attached as appendix).
- b. Drs. Arnold, Lambeth and Petros demonstrated that Nox1 triggers the angiogenic switch in prostate cancer (Reference 7, attached as appendix).
- c. Dr. Arnold demonstrated that NOX5 regulates growth and apoptosis of prostate cancer (Reference 12, attached as appendix).

4. Drs. Petros, Marshall and Wallace demonstrated the age-associated accumulation of mitochondrial DNA (mtDNA) mutations in prostate cancer (Reference 6, attached as appendix).

5. Drs. Petros, Young and Marshall showed that the expression of beta defensin 1 (initially found on tumor gene expression array analysis) is decreased in prostate and renal cancer, suggesting that this may be one of the chromosome 8p tumor suppressor genes.

6. Drs. Petros and Marshall identified a novel gene (PrLZ) that may be one of the oncogenes on chromosome 8q, accounting for the frequent observation of amplification of this chromosome in clinical prostate cancer (Reference 14, attached as appendix).

Reportable Outcomes:

I. Published manuscripts (14 published manuscripts, listed in references and explained in “body and key research accomplishments”).

II. Grants

Note: Dr. Petros is PI or co-investigator on all of these grants. Those listed below as “A”, “B” and “D” had data generated by this DOD grant included in preliminary data and are thus directly consequent to the funding of this award. The center grant “C” below was enabled by the consortium developed in this DOD award, as was the program project grant (“A” below).

A. 1PO1 CA98912 (Chung)	08/01/03 – 07/31/08			
28% (Co-PI and Project Leader)	\$ (Annual, Direct)			
Prostate Cancer Bone Metastasis: Biology and Targeting				
B. 1RO1 CA96994-01 (Petros)	08/01/02 – 07/31-07			
30% (PI)				
NIH	\$1, (Total)	\$		(Current)
Mitochondrial DNA Mutations in Prostate Cancer				
C. 1 P20 CA103735 (Simons)	07/01/03 – 06/30/08			
10% (Prostate Cancer Program Co-Director)				
NIH	\$ (Total)	\$		(Current)
Winship Cancer Institute, Emory University Planning Grant				
D. 1RO1 CA84138 (Lambeth)	01/05/00 – 12/31/04			
8% (Collaborator)				
NIH	\$ (Total)	\$		(current)
Mox1: A novel mitogenic oxidase				

III. Abstracts:

Petros, JA, Sun CQ, Irons H, Donald C, Amin MB, Lim SD, Hosseini S, Marshall FF, Wallace DC. Mitochondrial DNA mutations in prostate cancer. J Urol. 165 (5) Supl: 137, A563, 2001

Jessie BC, **Sun QC, Irons H, Marshall FF, Wallace DC, Petros JA.** Accumulation of mitochondrial DNA deletions in the aging prostate. J Urol. 165 (5) Supl: 138, A567, 2001

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Sun QC, Irons H, Arnold R, Lambeth JD, Marshall FF, Petros JA. Nox1 transfected prostate cancer cell line DU145 shown increased tumorigenesis and proliferation rates. Proceedings of the American Association for Cancer Research 42: 527, A2838, 2001.

Jessie BC, **Sun QC, Irons H, Marshall FF, Simons J, Wallace DC, Petros JA.** Accumulation of mitochondrial DNA deletions in the aging prostate. Proceedings of the American Association for Cancer Research 42: 862, A4624, 2001.

IV. Cell lines:

Cell Lines:

Wu (Project 3): Several cell lines derived from LNCaP that express MUC-18

Petros (Project 2): Cybrid cell lines with the 8993 mutation in PC3.

Arnold (Project 1): Nox-1 expressing lines derived from DU-145.

Conclusions:

1. This DOD center award was successful in both novel research discoveries and initiation of a vital multidisciplinary prostate cancer research group at Emory.
2. Multiple grants have been funded as a direct result of this award.
3. Multiple scientific manuscripts have resulted from this work.
4. The investment made by the US government in this award has been substantially leveraged to allow ongoing discovery well beyond the period of the award

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